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REMARKS

Upon entry of the amendment, claims 2-14 will be pending. Claims 9, 10, 13, and 14 have been withdrawn.

Regarding the Amendments

Claim 2 has been amended to clarify the subject matter regarded as the invention. As such, the amendment does not add new matter.

Rejections under 35 U.S.C. § 112

The rejection of claims 2-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention is respectfully traversed.

It is acknowledged in the Office Action that the claims make clear that a GDF-5 specific antibody binds a GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO:10 and SEQ ID NO:13. It is alleged, however, that claims 2-14 are indefinite because the terms "growth differentiation factor-5 (GDF-5)" is recited in the preamble of claim 2, and the terms "GDF-5 specific antibody" and "the GDF-5 polypeptide" are recited in the claim body, and it is therefore not clear whether these terms are limited to GDF-5 "having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13".

In regard to the term "growth differentiation factor-5 (GDF-5)" as recited in the preamble of claim 2, Applicants submit that the function of this term is in stating the purpose or intended use for the invention, and that it is the claim body, in this instance, that clearly defines the scope of the claimed invention. The Examiner's attention is respectfully drawn to MPEP § 2111.02, which states the following:

> "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's

> limitations, then the preamble is not considered a limitation and is of no significance to claim construction."

As such, Applicants submit one skilled in the art reading the claim preamble in the context of the entire claim would understand that claim 2-14 are directed to methods of "comparing expression of growth differentiation factor-5 (GDF-5)...having the amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13".

In regard to the terms "said GDF-5 specific antibody" and "the GDF-5 polypeptide", Applicants point out that these terms follow and specifically refer to the phrase "a GDF-5 specific antibody that specifically binds a GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13", which provides the requisite antecedent basis. As such, Applicants submit that one skilled in the art, viewing the claims, would clearly understand the metes and bounds of the claimed invention. Accordingly, it is respectfully requested that this rejection be removed or, alternatively, that the basis of this rejection of claims 2-14 be clarified.

Claims 2-14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because claim 2 recites the terms "GDF-5 specific antibody" and "specifically binds". The rejection is respectfully traversed.

Applicants point out that claim 2 clearly recites that "a GDF-5 specific antibody" is an antibody that "specifically binds a GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13". Applicants submit that the terms "specific" and "specifically binds" as used in regard to an antibody are well understood in the art that refer to the ability of an antibody to distinguish, by selective binding, a target immunogen from other antigens (see, e.g., Exhibit A, pages 54-57 from "The Encyclopedia of Molecular Biology", 1994; see p.54).

Furthermore, Applicants point out that the Examiner specifically acknowledges that the claims "make it clear that the antibody binds a GDF-5 having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13" (Office Action mailed 4/20/2004, page 2,

lines 21-23). As such, it is submitted that a skilled artisan would clearly recognize that the terms "GDF-5 specific antibody" and "specifically binds" refer to an antibody capable of selectively binding a GDF-5 polypeptide having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13. Accordingly, it is requested that this rejection be removed or, alternatively, that the basis of the rejection of claims 2-14 be clarified.

Claims 2-14 are additionally rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because claim 2 recites the terms "altered expression" and "comparable specimens obtained from normal subjects", and because these terms are relative with respect to each other.

It is initially noted that Claim 2 has been amended to remove the term "comparable specimen obtained from normal subjects" and instead require that "the specimen of the subject suspected of having altered expression of the GDF-5 polypeptide and the specimens of normal subjects are obtained from the same type of tissue." As such, one skilled in the art would recognize that a specimen of a subject suspected of having altered expression of the GDF-5 polypeptide may be selected from various types of tissue, for example, adult uterine tissue or placenta, brain, thymus, lung, kidney, and adrenal gland, or, in embryos, skeletal tissue, and that such specimen should be compared with the level of expression in a control specimen, such as one from a "normal" subject, obtained from the same type of tissue.

With respect to the term "normal subjects", it is alleged that this term is unclear because "normal" is a relative term and is not defined by the claim or the specification. First, Applicants submit that, based only on the plain meaning of the term, it would be clear to one skilled in the art, reading the current claims, that the term "normal", as it applies to "normal subjects", refers to healthy ("normal") individuals and that expression of the invention GDF-5 polypeptide in a "normal subject" includes expression occurring naturally and not due to disease. In support of this position, Applicants submit the definition of the term "normal" as found in the *Merriam Webster Medical Dictionary*, a copy of which is submitted herein as Exhibit B (see

definition 2). Accordingly, Applicants submit that the meaning of the term, as used in the claims, would be clear to the skilled artisan in light of its plain meaning.

Second, it is submitted that absent any inconsistency between the use of the term in either the claims or the specification, or with the ordinary meaning, there is no reason to believe that the term would be unclear to those skilled in the art. In this regard, Applicants point out that, while provisions of the present specification are cited in the Office Action, the Examiner has failed to identify a single instance in the specification where the term "normal" is used in a manner inconsistent with its plain meaning. In contrast, Applicants have identified numerous examples in the specification of "normal" individuals, including expression patterns of the invention GDF-5 polypeptide in a variety of healthy ("normal") adult tissues (Example 2) and in healthy ("normal") embryonic tissues (Examples 2 and 3). As such, it is submitted that the term "normal" is used in claims 2-15 in a manner consistent with its plain meaning and, absent objective evidence to the contrary, there is no reason to believe that the term "normal subject" recited in the current claims would be unclear to the skilled artisan.

With regard to the term "altered expression", Applicants point out that "altered expression" of the GDF-5 polypeptide is clearly defined in the claims as an increased or decreased level of GDF-5 specific antibody binding to the specimen of the subject suspected of having altered GDF-5 expression compared to binding to specimens of normal subjects. As such, it is submitted that a skilled artisan, having a clear understanding of the term "normal subjects" for the reasons set forth above, would similarly understand the term "altered expression" regardless of whether the term is "relative". Accordingly, removal of this ground of the rejection is respectfully requested.

It is further alleged that the metes and bounds of the claimed invention are unclear because the specification recites the term "suspect cell" but does not provide adequate guidance to determine when a cell is suspect. First, Applicants wish to clarify that the claims do not recite the term "suspect cell" but, instead, recite to "a specimen of the subject suspected of having

altered expression of the GDF-5 polypeptide". In this respect, and as discussed in detail in the following section (regarding the enablement rejection) the specification clearly discloses examples of such subjects (see, e.g., page 6, line 19, to page 7, line 14). As such, the skilled artisan, viewing the subject application, clearly would have been apprised of subjects that can have such GDF-5 associated disorders and for whom "a specimen" can be examined according to the present methods. As such, it is submitted that the specification provides adequate guidance such that one skilled in the art would know a subject suspected of having altered expression of the GDF-5 polypeptide, and would know the appropriate specimen to be examined.

For the reasons set forth above (see, also, below), it is submitted that the subject matter of claims 2 to 14 is clearly defined such that the skilled artisan would know the metes and bounds of the claimed invention. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

The rejection of claims 2-14 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

It is acknowledged that the specification is enabling for a method of detecting GDF-5 having an amino acid sequence as set forth in SEQ ID NO:10 or SEQ ID NO:13 in uterine, endometrial, or skeletal tissue. It is alleged, however, that the specification does not provide enablement for detecting altered expression of GDF-5 in a person in need thereof or in the subject suspected of having altered expression of the GDF-5. Specifically, it is alleged that the specification does not provide examples of subjects suspected of having altered expression of GDF-5 and, therefore, lacks guidance in regard to such subjects.

Applicants submit that the specification clearly discloses that GDF-5 is expressed primarily in uterine tissue (Example 2) and skeletal tissue (Example 3), at lower levels in other adult tissues (page 25, lines 7-10). Further, it is known in the art that other GDF polypeptides such as GDF-8 (myostatin) have an effect on the tissue in which they are expressed (e.g., muscle). As such, the skilled artisan would have known that tissues having altered growth and

differentiation, including both the tissues in which GDF-5 is primarily expressed (uterine and skeletal) as well as tissues in which GDF-5 is expressed at lower levels, would reasonably be suspected of having altered expression of GDF-5.

In addition, the specification provides numerous examples of disorders associated with altered expression of GDF-5 such that the skilled artisan would have known subjects and specimens to be examined according to the methods of the invention. For example, the specification discloses that various uterine disorders, such as due to hypertrophy, hyperplasia, the presence of ectopic tissue, or uterine neoplasms, as well as endometriosis (page 6, lines 19-25); developmental anomalies (page 6, lines 25-27; Example 3); and abnormalities in bone formation, such as various bone dysplasias (page 7, lines 1-14, Example 4) can be associated with altered expression of GDF-5, and further discloses and that GDF-5 can be involved in collagen formation similar to other TGF-β family members (page 7, line 24, to page 8, line 4). In this respect, Applicants submit that such roles for GDF-5 are well known in the art, as evidenced, for example, by Exhibit C, which is data sheet for BMP-14 (GDF-5 also is known as BMP-14; see Exhibit D) provided by Research Diagnostics, Inc.; see Exhibit C, page 3/5; see, also, Exhibit E, describing the role of GDF-5 (BMP-14) as a principal initiator of cartilage development, page 1/2).

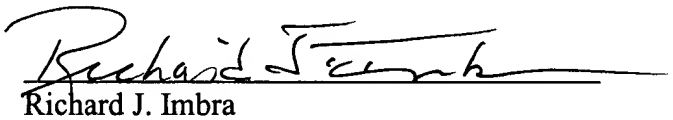
As such, it is submitted that one skilled in the art, viewing the specification, would have known of subjects suspected of having altered expression of GDF-5 and, therefore, would have known how to practice the claimed methods without undue experimentation. Accordingly, it is respectfully requested that the rejection of claims 2 to 14 under 35 U.S.C. § 112, first paragraph, be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

No fee is deemed necessary in connection with the filing of this paper. However, if a fee is required, the Commissioner is hereby authorized to charge any required fee associated with the filing submitted herewith, or credit any overpayments, to Deposit Account No. 50-1355.

Respectfully submitted,

Dated: July 20, 2004



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Enclosures: Exhibits A to E

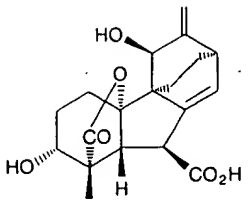
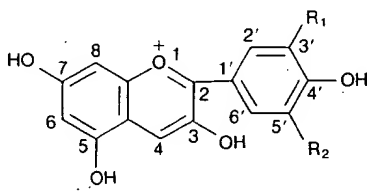


Fig. A39 Structure of antheridic acid, an antheridiogen produced by *Anemia* species.

berellins, such as GA_9 and GA_{73}, from *Lygodium japonicum*, and gibberellins in which the C and D rings have been rearranged, from *Anemia* species. They are among the most active plant hormones; GA_{73} methyl ester induces antheridial formation in *L. japonicum* at 10^{-14} M.

Yamane, H. (1991) In *Gibberellins* (Takahashi, N. et al., Eds) 378–388 (Springer-Verlag, Berlin).

anthocyanins Water-soluble glycosides of hydroxylated 2-phenylbenzopyrilium salts (anthocyanidins), pigments responsible for many of the pink, red, blue and black colours of flower petals, pollen, leaves and fruits.



R_1, R_2 = H, OH, or OCH_3.

The 3-OH and, more rarely, 5-OH groups are glycosylated. The range of colours is due to different anthocyanidins (R_1, R_2 vary), different sap pH, complexes with metal ions and copigmentation with other flavonoids. They accumulate in VACUOLES of plant cells.

Antibodies

ANTIBODIES (immunoglobulins) are multifunctional GLYCOPROTEINS produced by the immune system of vertebrates and are essential for the prevention and resolution of infection by microorganisms. They are structurally highly variable molecules that carry out this function by recognizing and binding to particular molecular configurations on invading microorganisms and their products, each antibody being able to bind only one or a small number of related molecular configurations [1–3]. Any molecule or material bound specifically by an antibody is termed an antigen, and many different substances can act as antigens, not only those found on pathogenic microorganisms. The protective role of antibody is determined by the ability of specific antigen–antibody complexes to activate one or more of the many effector mechanisms that contribute to the neutralization, destruction and elimination of the infecting microorganism.

Antibodies are secreted by the B CELLS of the immune system after terminal differentiation to PLASMA CELLS (*see* B CELL DEVELOPMENT). The molecular mechanisms that result in the generation of an antibody REPERTOIRE of almost infinite antigen recognition diversity are described in the articles on GENERATION OF DIVERSITY, IMMUNOGLOBULIN GENES and GENE REARRANGEMENT elsewhere in this volume. This article focuses on the basic structure and function of antibodies; further details of the structure of the immunoglobulin antigen-binding site at the molecular level will be found in IMMUNOGLOBULIN STRUCTURE.

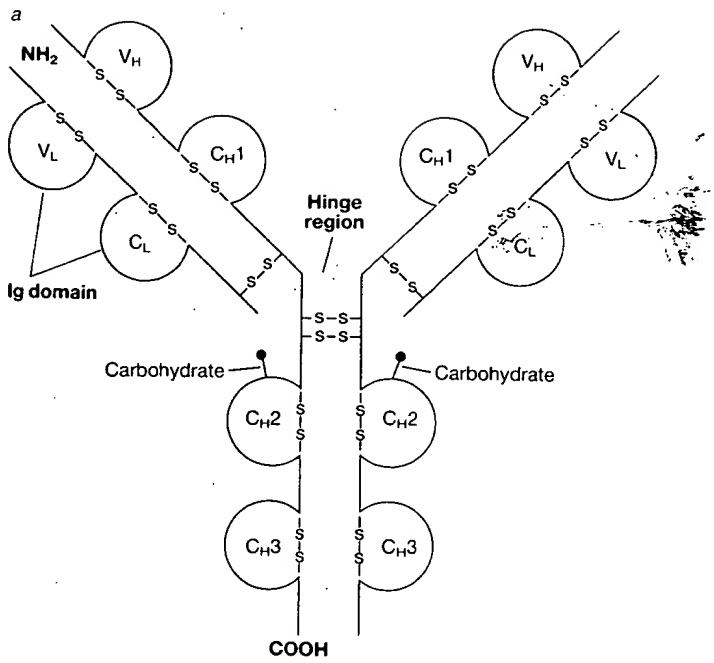
The immunoglobulin fraction of blood consists naturally of a polyclonal mixture of many different types of antibodies specific for the different antigens the individual has been exposed to (i.e. they originate from many different clones of antibody-producing cells). MONOCLONAL ANTIBODIES are antibodies of a single specificity (i.e. they originate from a single clone of antibody-producing cells). Our current understanding of the structure and function of antibody molecules has resulted from study of specific antibody isolated from the sera of immunized experimental animals, or of polyclonal and monoclonal immunoglobulin of unknown antigen specificity. Long before the advent of recombinant DNA techniques, the isolation and purification of naturally occurring monoclonal immunoglobulins — the products of murine PLASMACYTOMAS or human MYELOMA — allowed the definition of the immunoglobulin isotypes (see below) and the generation of a library of amino-acid sequence data from which the structural basis for antibody specificity was determined.

The elucidation of antibody structure

The four-chain structure

The introduction of the technique of ion-exchange CHROMATOGRAPHY in the 1950s allowed rabbit IgG, the most abundant class of immunoglobulin in immunized animals, to be purified from serum in a single step. As specific antibody responses were also readily induced in rabbits, this laboratory animal was used in many of the early definitive investigations. Studies of the pattern of protein fragmentation following digestion of antibody with the enzyme papain, by Rodney Porter, and of the polypeptide chain components, by Gerry Edelman, led Porter to propose the four-chain structure for rabbit IgG in 1959 (see Fig. A40). This model proposed that each individual IgG molecule is composed of two light chains of M_r 25 000, of identical amino-acid sequence, and two heavy chains of M_r 50 000 also of identical amino-acid sequence. The light chains are covalently bound to the heavy chains through a single disulphide bridge and the heavy chains are similarly covalently linked to each other through one or more disulphide bridges (the number of disulphide bridges between heavy chains varies with isotype and species). Reduction of the disulphide bridges does not result in dissociation of the molecule, under physiological conditions, owing to the presence of multiple light–heavy and heavy–heavy interchain noncovalent bonds.

The 150K IgG molecule could be digested by papain to yield



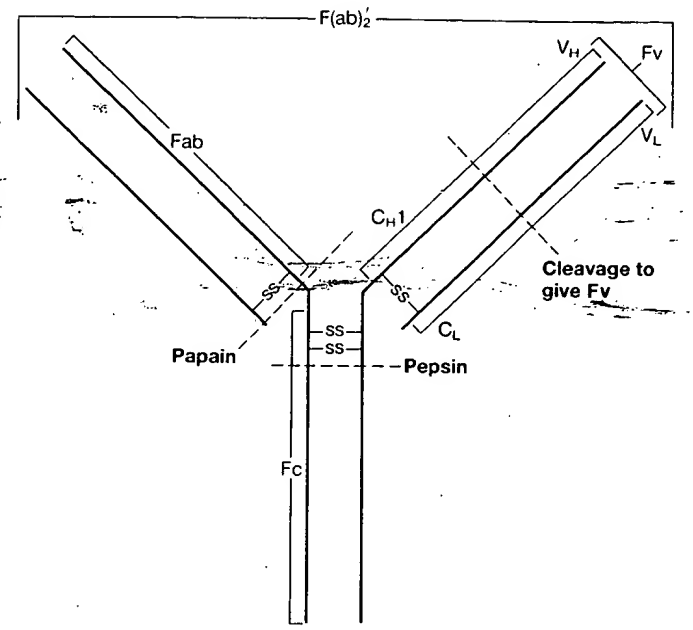


Fig. A41 Fragments of an antibody molecule obtained by enzymatic digestion. Digestion by papain produces two types of fragment: Fc, fragment crystallizable; Fab, fragment antigen binding (containing one antigen-binding site). Digestion with pepsin produces F(ab)′, a fragment containing two antigen-binding sites. Fv, the V_LV_H heterodimer, can also be produced by cleavage or is now obtained by genetic engineering.

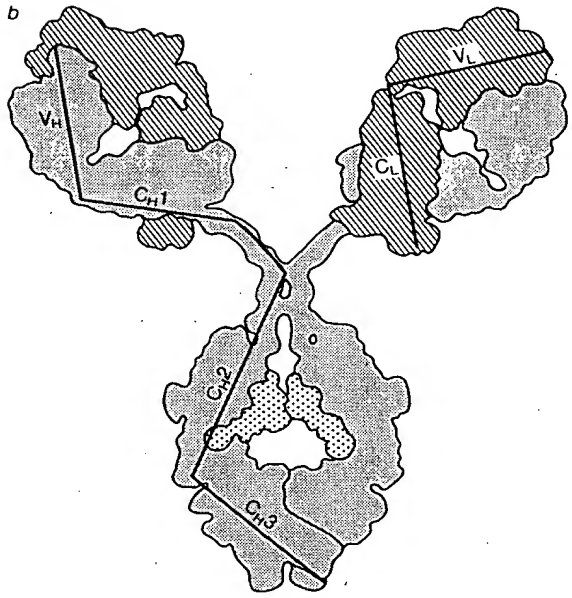


Fig. A40 *a*, Schematic representation of an immunoglobulin molecule (IgG). V_H and V_L are the variable domains of heavy and light chains respectively. C_L is the light chain constant region. C_H1, C_H2, and C_H3 are heavy chain constant region domains. S–S, disulphide bond. See text for further information. *b*, Diagrammatic representation of a human IgG molecule. The heavy chains are shaded in grey, the light chains hatched, and carbohydrate stippled (*see also* Plate 6*d*).

50K fragments (Fig. A41). Dialysis of the digestion products resulted in the formation of protein crystals that accounted for one-third of the original protein mass; this was named the Fc fragment as it was the 'fragment crystallizable'. The remaining fragments, accounting for two-thirds of the original protein mass, were shown to bind antigen in an equivalent manner to the original molecule and these fragments were named the Fab fragments as they were antigen binding. Each antibody monomer has two identical antigen-binding sites and is thus divalent. The open and flexible polypeptide structure between the Fab and Fc regions is referred to as the hinge region. The equivalent regions of all antibody molecules are referred to by this common nomenclature although their Fc regions may never have been isolated in crystalline form. Rodney Porter and Gerry Edelman were awarded the Nobel Prize in 1972 for their pioneering studies that allowed the basic structure–function characteristics of antibody molecules to be understood.

Immunoglobulin (antibody) isotypes

In humans and the higher mammals five classes of immunoglobulin have been defined: IgG, IgM, IgA, IgD, and IgE and additionally, in humans, four subclasses of IgG and two subclasses of IgA. Since immunoglobulins of each class and subclass are present in all normal individuals they are referred to as isotypes (as distinct from the immunoglobulin ALLOTYPES and IDIOTYPES). The five different classes are determined by the type of heavy chain involved (termed γ, μ, α, δ, and ε respectively). Originally distinguished by immunological criteria (i.e. as distinct antigens), each isotype was later shown to be characterized by its amino-acid sequence and to be the product of a different gene segment (C genes, *see* IMMUNOGLOBULIN GENES).

The logic of immunoglobulin nomenclature may not be readily apparent and arises from the methods initially used to distinguish

the different classes. Initially, two distinct forms of antibody were recognized — the high molecular weight macroglobulins and the lower molecular weight gammaglobulins — hence IgM and IgG (gamma refers to electrophoretic mobility). When a further class was recognized it was decided to systematize the nomenclature and to call this new class IgA and it was suggested that IgM and IgG might be redesignated IgB and IgC. Thus, discovery of two further classes gave us IgD and IgE. However, the suggestion to rename IgM and IgG was never adopted. Two types of human immunoglobulin light chain were also defined by their distinct antigenicity and named kappa (κ) and lambda (λ) to denote their discovery by Korngold and Lipari.

Constant and variable regions

In the 1960s it became appreciated that BENCE-JONES PROTEIN, excreted in the urine of patients with multiple MYELOMA, represents an overproduction of light chain by the malignant clone of cells. Consequently it was homogeneous and readily purified for structural analysis. Sequence analysis of Bence-Jones protein from different individuals revealed that amongst κ chains the amino-acid sequence of the N-terminal 110 residues was always different whereas the sequence of the C-terminal 110 residues was constant. These regions or domains were therefore termed the variable (V) region (in this case V_κ) and the constant (C) region (C_κ); λ chains are similarly composed of V and C regions. Comparison of the sequences of heavy chains of the same isotype showed that they also comprised a variable N-terminal region of 110 amino-acid residues whereas the remainder of the sequence is constant and defines the isotype (Fig. A40*a*). Minor sequence differences between the C regions of immunoglobulins of the same isotype from different individuals allow the definition of allotypes (allelic variants of each C gene), first defined serologically using ALLOANTISERA.

In 1969 Edelman's group published the first complete covalent structure of an antibody molecule (i.e. the amino-acid sequences of the light and heavy chains). Examination of the amino-acid sequence revealed repeating motifs of ~110 amino-acid residues. Each is termed an immunoglobulin homology region or immunoglobulin domain (Fig. A40) and is now known to be the product of an individual EXON (*see* IMMUNOGLOBULIN GENES). This finding also suggested that the prototype immunoglobulin molecule may have been a protein of 110 amino acid residues and that subsequent gene duplications and the evolution of mechanisms for joining (splicing) gene segments could account for the emergence of antibody molecules (*see* IMMUNOGLOBULIN SUPERFAMILY). The hinge region was seen to have a distinct characteristic sequence which included the inter-heavy chain disulphide bridges and to be rich in proline residues, thus accounting for the open structure. The Fab and Fc regions are compact globular structures each composed of four paired homology domains.

Each domain has a characteristic tertiary structure that is referred to as the immunoglobulin fold (Fig. A42). It is comprised of two surfaces of antiparallel β-pleated sheet linked through a disulphide bridge. Hydrophobic residues are packed into the internal space and hydrophilic residues are exposed on the surface of the molecule.

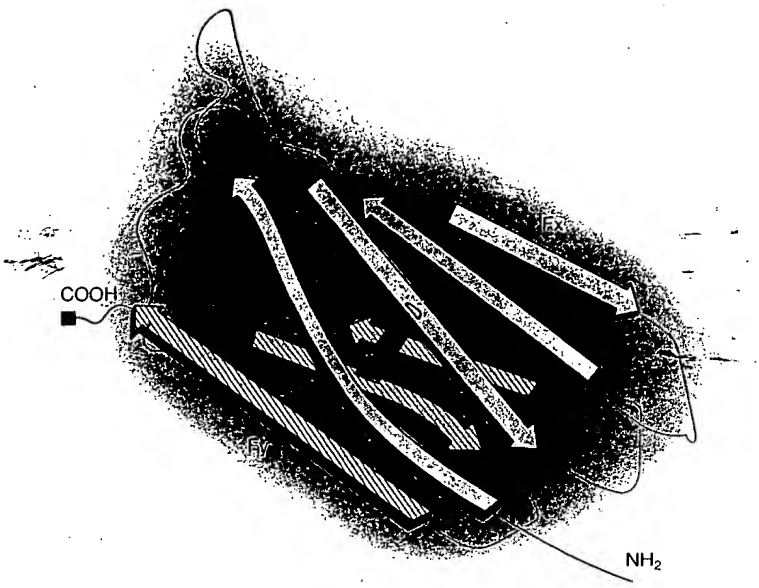


Fig. A42 The immunoglobulin fold of an immunoglobulin constant domain. The upper Fx face is formed by four strands of antiparallel β-pleated sheet; the lower Fy face by three. The hydrophobic core is stippled grey; the outer surface is hydrophilic.

Antigen recognition/binding

Comparisons of V region sequences showed that variability was not uniformly distributed but concentrated into three areas that were named the HYPERVARIABLE REGIONS. The crystal structure of an antigen-binding Bence-Jones protein demonstrated that the residues of the hypervariable regions (e.g. residues 25-35, 50-55, 95-100 in the light chain) are contact residues for antigen binding and hence they are now referred to as the COMPLEMENTARITY DETERMINING REGIONS (CDR) to indicate their functional role. It was appreciated that the more constant sequence of residues outside of the CDRs was required to maintain the essential immunoglobulin fold which results in the CDRs being brought into three-dimensional proximity with each other. These residues are referred to as the framework regions. The same pattern is observed for heavy chains, and in the intact antibody molecule the light and heavy chain CDRs form a continuous surface for contact with antigen (*see* IMMUNOGLOBULIN STRUCTURE).

Idiotypes

The unique structural features of the antigen-binding site of an antibody molecule, generated by the CDRs, may be antigenic within the same or heterologous species and result in the production of anti-idiotypic antibodies. The idiotype of an antibody molecule is the sum of all of the individual antigenic determinants (idiotopes) related to the binding site structure. The demonstration of anti-idiotypic responses within the same strain of mice and/or the production of auto anti-idiotypic responses led Niels Jerne to propose that immune regulation may be determined by a network of idiotype–anti-idiotype interactions [4].

Further analysis of framework sequences allowed the identification of immunoglobulins having a high degree of homology such that they could, conceivably, be encoded by a common germ-line gene requiring only POINT MUTATIONS to encode for the observed sequence. These related sequences were taken to define V gene subgroups (*see* IMMUNOGLOBULIN GENES) and antisera were also developed that allowed their serological detection.

Genetically engineered antibodies

Occasionally, it has been possible to derive a subfragment of the Fab fragment — the Fv fragment — composed of the light and heavy chain V regions only. It is a heterodimer formed by noncovalent bonds and having the same antigen-binding specificity and affinity as the parent molecule. Such molecules can now be readily constructed using genetic engineering techniques [5]. The finding that the V region of the heavy chain makes the major contribution to the antigen-binding affinity has led to the production of recombinant proteins comprising the variable region of the heavy chain only (Hv fragments) as antigen specificity reagents.

As evidenced above, GENETIC ENGINEERING techniques have been widely applied to antibody molecules. Our need to understand fully the profile of biological activities of each of the human antibody isotypes has been significantly advanced by studies using chimaeric immunoglobulins. They are constructed using murine genes encoding antibody specificity (V regions) and human C region genes encoding the human isotypes. A further development allows murine antibodies to be 'humanized' by 'grafting' the CDR of specific murine antibodies (*see* MONOCLONAL ANTIBODIES) into the desired human isotype background. This technology finds its most appropriate application when the antibodies are used for *in vivo* diagnostic or therapeutic purposes. Conservative PROTEIN ENGINEERING approaches are being applied to alter the specificity or affinity of antibody molecules and to modulate Fc effector functions. This will permit the rational design of 'customized' antibody molecules having a profile of activities considered to be optimal for a given application.

Antibody effector functions

Antibodies may be regarded as transducer molecules that relay a 'message' to an effector system. The message is the presence of antigen in the form of specific immune complexes (antigen–antibody complexes). Cellular receptors specific for the Fc region of each of the antibody classes (FC RECEPTORS) have been reported on a variety of cells. Those expressed on T CELLS are thought to be involved in immune regulation but they are structurally and functionally poorly defined. Also ill defined is the placental Fc receptor that facilitates specific transport of IgG from the mother to the foetus. By contrast Fc receptors expressed on leukocytes are well defined and characterized. There are three Fc receptors for human IgG, distinguished by the preferred notation huFcγRI, huFcγRII, and huFcγRIII (hu standing for human); receptors for IgE and IgA are similarly referred to as huFcεRI, huFcεRII, and huFcαR respectively. Interactions of antigen–antibody complexes with Fc receptors on macrophages may activate the release of proteolytic enzymes, reactive oxygen species and phagocytosis (*see* ENDOCYTOSIS). Complexes of antigen with IgG, IgM or IgA may activate COMPLEMENT through one or both of two pathways; the classical pathway initiated by the activation of C1 and the alternative pathway initiated by the activation of C3. The ensuing cascade of reactions may result in the release of inflammatory mediators, phagocytosis via complement receptors, lysis of sensitized cells or bacteria by the production of holes in their membranes, etc. The interaction site for the first component of complement, C1, has been mapped to the Fc region of IgG and IgM isotypes.

The activation of the IGE RECEPTOR on mast cells results in the release of chemical mediators such as histamine and is responsible for immediate hypersensitivity reactions and allergies.

R. JEFFERIS

See also: T CELL RECEPTORS; T CELL RECEPTOR GENES.

1 Burton, D.R. (1985) Immunoglobulin G: Functional sites. *Mol. Immunol.* **22**, 161–206.
2 Jefferis, R. (1991) Structure–function relationships in human immunoglobulins. *Netherlands J. Med.* **39**, 188–198.
3 Roitt, I. (1991) *Essential Immunology*, 7th edn (Blackwell Scientific Publications, Oxford).
4 Jerne, N.K. (1984) Idiotype networks and other preconceived ideas. *Immunol. Rev.* **79**, 5–24.
5 Winter, G. & Milstein, C. (1991) Man-made antibodies. *Nature* **349**, 293–299.

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antibody combining site The antigen recognition and binding site on an ANTIBODY, the region of the molecule which binds a specific antigenic determinant (EPITOPE) owing to molecular complementarity. The combining site is formed by the noncovalent association of the N-terminal domains of a light and a heavy chain such that the hypervariable or COMPLEMENTARITY DETERMINING REGIONS are brought together in space to form a continuous protein surface. Each Fab region of an antibody molecule contains one combining site. *See*: IMMUNOGLOBULIN STRUCTURE.

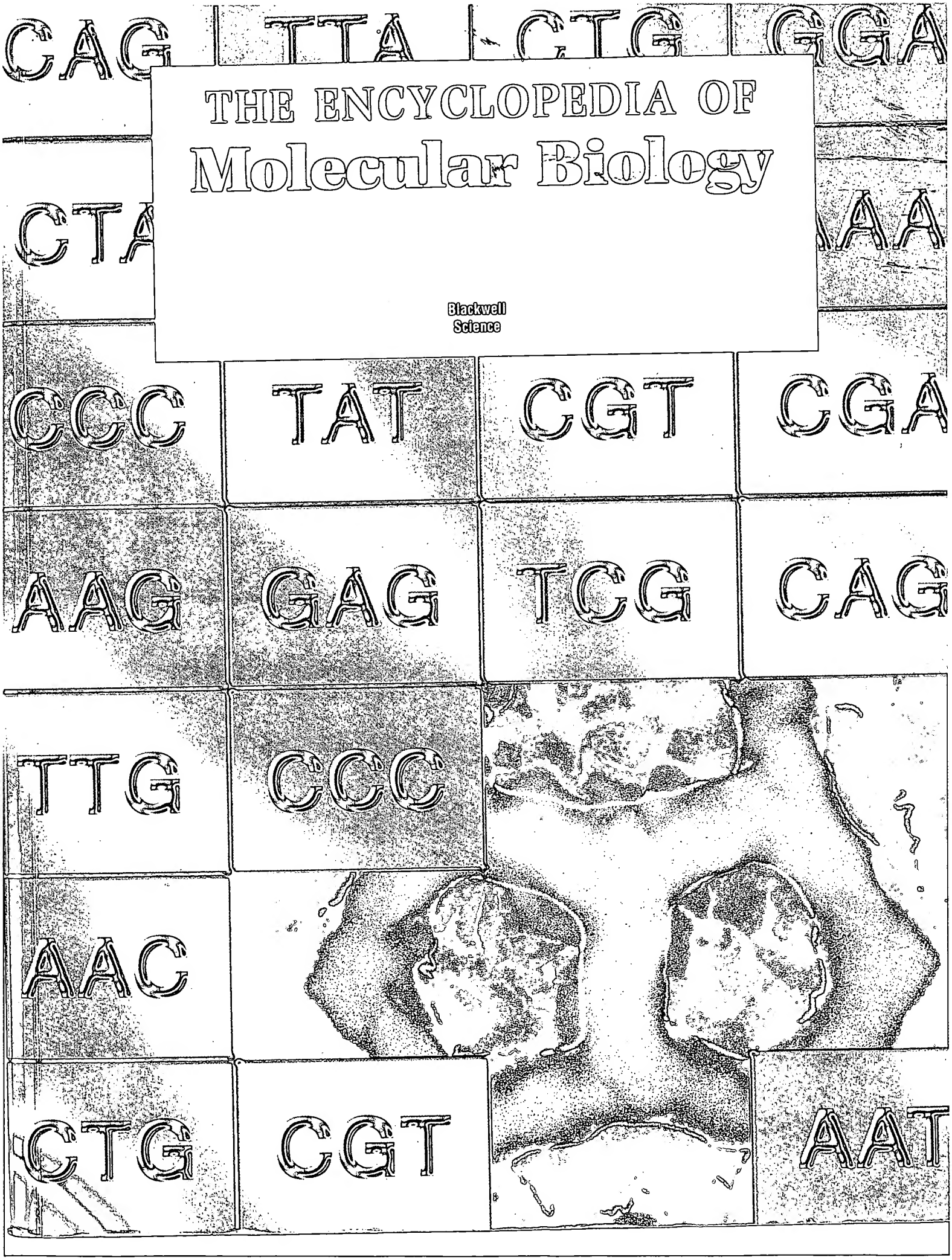
antibody diversity *See*: GENERATION OF DIVERSITY.

antibody engineering The manipulation or mutation of the DNA that encodes antibodies to generate molecules not found in nature. A minimally engineered antibody may result from a single base change leading to a single amino acid replacement in the protein with a change in functional activity, for example, antigen specificity, affinity or an interaction site for triggering of effector functions. Humanizing of animal antibodies represents maximally engineered molecules in which the specificity of an animal antibody is 'transferred' to a human immunoglobulin by exchange of all the COMPLEMENTARITY DETERMINING REGIONS.

Winter, G. & Milstein, C. (1991) *Nature* **349**, 293–299.

anticoding strand The strand of a double-stranded DNA that is transcribed into RNA during TRANSCRIPTION.

anticodon The sequence of three nucleotides in a TRANSFER RNA molecule which is complementary to a specific CODON in mRNA.



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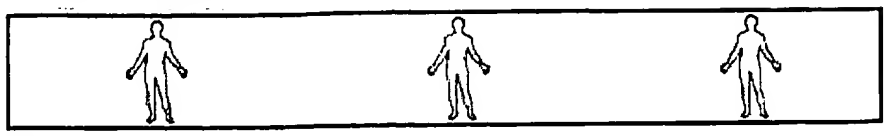

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normal[2,noun]
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normal salt solution
physiological saline

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Main Entry: **[1]nor·mal**
Pronunciation: 'nor-m&l
Function: *adjective*
1 a : according with, constituting, or not deviating from a norm, rule, or principle **b :** conforming to a type, standard, or regular pattern
2 : occurring naturally and not because of disease, inoculation, or any experimental treatment <*normal* immunity>
3 a : of, relating to, or characterized by average intelligence or development **b :** free from mental disorder : SANE **c :** characterized by balanced well-integrated functioning of the organism as a whole
4 a *of a solution* : having a concentration of one gram equivalent of solute per liter **b :** containing neither basic hydrogen nor acid hydrogen <*normal* phosphate of silver> **c :** not associated <*normal* molecules> **d :** having a straight-chain structure <*normal* pentane> <*normal* butyl alcohol>
- **nor·mal·ly** /'nor-m&-lE / *adverb*

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-see also BMP antibodies (see BMP-2 & BMP-14)

Recombinant Human BMP-2

Description: Human Bone Morphogenetic Protein-2 (BMP-2) is a disulfide-bonded homodimeric protein with an apparent molecular weight of 26 kDa. BMP-2 regulates similiarly to its nearest homologue BMP-4 diverse fundamental processes during embryonic development: BMP-2 and other BMP proteins have great potential for medical therapeutic applications, in particular because they allow or at least accelerate the ossification of extensive bone lesions. BMP-2 lacks the natural N-terminus which results in a 15-20 fold increase of specific activity. BMP-2 is a heparin binding protein.

Source:	E. coli
Molecular Weight:	26 kDa
Specific activity:	5 x 10 4 units/mg
Purity:	> 95% by SDS-PAGE and visualised by silver stain
Endotoxin level:	< 0.1 ng per mg of BMP-2
Stabilizer:	none
Buffer:	none
Formulation:	lyophilized

Biological Activity: The ED50 for the proteoglycan synthesis in embryonal chicken limb bud cells has been determined to be in the range of 20 to 30 ng/ml..

Reconstitution: The lyophilized BMP-2 is soluble in distilled water and most aqueous buffers at concentrations greater than 1 mg/ml when the pH is below 6.0. Above pH 6.0 the solubility is low, but could be increased by addition of 1 M NaCl or 30% 2-propanol or with 10mM Sodium Citrate buffer pH3.5

Stability: Lyophilised samples are stable for greater than six months at -20°C to -70°C. Reconstituted BMP-2 should be stored in working aliquots at -20°C. Avoid repeated freeze-thaw cycles!

Usage: BMP-2 is offered for research use. Not for drug use. Not for human use!

Catalogue number: RDI-200-002 $400.00 $350.00/vial 5+ Size: 25 µg

RDI-200-002X $700.00/50ug vial

Bulk quotes on request

Literature: [Wozney et al., Science 242:1528, 1988; Ruppert et al., Eur J Biochem 237 :295, 1996]

DATA SHEET:recombinant Human BMP-2

-BMPs (bone morphogenetic proteins) belong to the TGF-beta superfamily of structurally related signaling proteins. Members of this superfamily are widely represented throughout the animal kingdom and have been implicated in a variety of developmental processes. Proteins of the TGF-beta superfamily are disulfide-linked dimmers composed of two 12-15 kDa polypeptide chains. As implied by their name, BMPs initiate promote and regulate bone development, growth, remodeling and repair. However, it is now clear that in addition to their role in bone and cartilage morphogenesis, BMPs are also involved in prenatal development and postnatal growth of eye, heart, kidney, skin and other tissues. In addition to its osteogenic activity, BMP-2 plays an important role in cardiac morphogenesis. It is also expressed in a variety of tissues such as lung, spleen, brain, liver, prostate ovary and small intestine. This recombinant human BMP-2 is a 26 kDa homodimeric protein consisting of two 115 amino acid polypeptide chains.

Catalog#: RDI-1202

Package Size: 10 micrograms $ 170.00 $150.00/2or more

500 micrograms $3600.00

$5,000/1MG cat#RDI-1202X

10 X 100ug=$5,600.00 cat#RDI-1202X1

MINI-PACK cat#RDI-1202p $75.00/2ug

Supplied: sterile filtered and the the protein was lyophilized from 10mM Sodium Citrate pH3.5(no additives)

Source: E. Coli

Purity: >98% by SDS-Page and HPLC analyses. Endotoxin level is less than 0.1ng per ug (1EU/ug).

Reconstitution: The lyophilized We recommend a quick spin followed by reconstitution in 10mM Sodium Phosphate pH3.5 OR diluting into water containing BSA (50µg of BSA per 1µg of protein) to a concentration of 0.1-1.0 mg/ml. Allow to set at least 30 minutes at 4 DEG C, tighten cap and rotate to reconstitute any material on sides of vial. If desired, you can centrifuge at 1000 rpm for 1 minute to

concentrate volume in bottom of vial. This solution can be diluted into water or other buffered solutions or stored at -4 DEG C for up to 1 week or at -20 DEG C for future use.

Note:the addition of 0.1% BSA to dilution buffers or dilution in sterile culture media is recommended to enhance stability and minimize absorption to vial. Ideally, maintain concentration >10ug/ml.

Storage: The lyophilized powder is stable at room temperature for a few weeks but it is best stored desiccated at -20 Deg C. Reconstituted human BMP-2 should be stored in working aliquots at -20 DEG C. AVOID FREQUENT FREEZE THAW CYCLES.

Reactivity: The ED50 as determined by the cytolysis of MC3T3-E1 cells is < 50ng/ml.

AA Sequence:

MQAKHKQRKR LKSSCKRHPL YVDFSDVGWN DWIVAPPGYH AFYCHGECPF

PLADHLNSTN HAIVQTLVNS VNSKIPKACC VPTELSAISM LYLDENEKVV

LKNYQDMVVE GCGCR

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DATA SHEET: **recombinant Human BMP-14/CDMP-1**

-BMPs (bone morphogenetic proteins) belong to the TGF-beta superfamily of structurally related signaling proteins. Members of this superfamily are widely represented throughout the animal kingdom and have been implicated in a variety of developmental processes. Proteins of the TGF-beta superfamily are disulfide-linked dimmers composed of two 12-15 kDa polypeptide chains. As implied by their name, BMPs initiate promote and regulate bone development, growth, remodeling and repair. However, it is now clear that in addition to their role in bone and cartilage morphogenesis, BMPs are also involved in prenatal development and postnatal growth of eye, heart, kidney, skin and other tissues. BMP-14/CDMP-1 is a principal initiator of cartilage development and is predominantly expressed in long bones during human embryonic development. Mutations in the BMP-14/CDMP-1 gene have been implicated in Grebe Syndrome, which is characterized by short stature, extra digits, short and deformed extremities, and in Hunter-Thompson type dwarfism. This recombinant Human BMP-14/CDMP-1 is a 27 kDa homodimeric protein consisting of two 121 amino acid polypeptide chains.

Catalog#: RDI-1201

Package Size: 10 micrograms $ 170.00 $150.00/2or more

500 micrograms $3600.00

$4,800/1MG cat#RDI-1201X

10 X 100ug=$5,400.00 cat#RDI-1201X1

MINI-PACK cat#RDI-1201p $75.00/2ug

Supplied: sterile filtered and the the protein was lyophilized from 10mM Sodium Citrate(no additives)

Source: E. Coli

Purity: >98% by SDS-Page and HPLC analyses. Endotoxin level is less than 0.1ng per ug (1EU/ug).

Reconstitution: The lyophilized We recommend a quick spin followed by reconstitution in water containing BSA (50µg of BSA per 1µg of protein) to a concentration of 0.1-1.0 mg/ml. Allow to set at least 30 minutes at 4 DEG C, tighten cap and rotate to reconstitute any material on sides of vial. If desired, you can centrifuge at 1000 rpm for 1 minute to concentrate volume in bottom of vial. This solution can be diluted into water or other buffered solutions or stored at -4 DEG C for up to 1 week or at -20 DEG C for future use.

Note:the addition of 0.1% BSA to dilution buffers or dilution in sterile culture media is recommended to enhance stability and minimize absorption to vial. Ideally, maintain concentration >10ug/ml.

Storage: The lyophilized powder is stable at room temperature for a few weeks but it is best stored desiccated at -20 Deg C. Reconstituted human BMP-14 should be stored in working aliquots at -20 DEG C. AVOID FREQUENT FREEZE THAW CYCLES.

Reactivity: The ED50 was determined by its ability to induce alkaline phosphatase production by ATDC-5 chondrogenic cells is 1-2ug/ml.

AA Sequence:

MAPSATRQGK RPSKNLKARC SRKALHVNFK DMGWDDWIIA PLEYEAFHCE

GLCEFPLRSH LEPTNHAVIQ TLMNSMDPES TPPTCCVPTR LSPISILFID

SANNVVYKQY EDMVVESCGC R

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AOFAS 2002 ANNUAL SUMMER MEETING

GDF-5 Deficiency in Mice Results in Delayed Achilles Tendon Healing: The Potential Use of Growth and Differentiation Factor (GDF) - 5 to Augment Tendon Healing

Anikar Chhabra, M.D.; Rashard Dacus, M.D.; Shephard Hurwitz, M.D.; Borjana Mikic, Ph.D. (Charlottesville, VA)

Introduction: Following Achilles tendon ruptures, there is often poor restoration of pre-injury function and strength. Multiple growth factors have been shown to play a role in the tendon repair process. The Growth and Differentiation Factors (GDFÕs) represent a distinct subset of the TGF-§ family best known for their role in joint formation and endochondral bone growth. Several recent pieces of evidence suggest that the GDFs may also be involved in tendon and ligament formation and repair. The goal of this study was to examine the effects of GDF-5/BMP-14 deficiency on tendon healing by characterizing the repair process in mice deficient in this particular growth factor. We hypothesized that GDF-5 deficient mice would exhibit an impaired healing response to Achilles tendon defects when compared to control mice.

Methods: The animal model used for these studies was the GDF-5 (-/-) brachypodism (bp) mouse. Phenotypically normal heterozygous (+/-) littermates and A/J (+/+) mice were used as controls. Mid-substance tenotomies and repairs of the left Achilles tendon were performed on 32 8-week-old male mice. As controls, sham operations were performed on the right legs. On postoperative days 3, 5, 7, 9, 12, 14, 28, and 42, the mice were euthanized and the repair tissue of the tenotomy was harvested for analysis. DNA, proteoglycan (GAG), and collagen (OHP) content were determined at each time point using standard biochemical assays. Each set of biochemical analyses was repeated at least twice on separate occasions to verify the results. Histologic characterization was performed using both H&E staining and Tri-chrome staining. Additional samples were analyzed histomorphometrically to determine quantitative trends in the percentage of healing tissue occupied by vasculature and adipocytes using point counting methods. Ultrastructural analyses was performed using 10 electron microscopy pictures per mouse to determine the fibril diameter, fibril numerical density, and fibril area fraction as a function of time. The biomechanical characteristics of the healing tissue at 5 weeks postoperatively were examined to determine the peak force to failure and stiffness of the repair tissue. For all quantitative analyses (biochemistry,

histomorphometry, ultrastructure, and biomechanics), data were expressed as a ratio of repair side values normalized to sham side values at each time point and analyzed statistically using a two factor ANOVA test.

Results: Based on biochemical measures, GDF-5 deficient mice displayed a delay of 5 Ð 9 days in attaining the peak values of normalized DNA, GAG, and collagen levels in healing Achilles tendon tissue when compared to controls. Statistically, the time dependent changes in all three biochemical measures were significantly affected by the presence or absence of GDF-5 ($p<0.001$). Histologically, GDF-5 deficient Achilles tendons also exhibited a delay in peak areal cell density and collagen reorganization. Histomophometrically, trends in the percentage of healing tissue occupied by blood vessels indicated that GDF-5 deficient tendons were delayed by approximately one week in the initial phase of vascularization ($p<0.05$). In addition, GDF-5 deficient healing tissue also exhibited a higher percentage of fatty tissue throughout the entire healing process ($p<0.05$). Ultrastructurally, fibril diameter is significantly smaller in the mutants when compared to controls, with larger differences occurring during the first 2 weeks of healing ($p<0.05$). The mutants have significantly more fibrils than controls per unit area at four and six weeks post-op ($p<0.05$). In the mutants, the fibril area fraction is significantly lower than the controls in the first 2 weeks of healing ($p<0.05$), but is comparable after 2 weeks. Biomechanically, the peak force to failure and the stiffness of the repair tissue in the GDF-5 deficient Achilles tendons remains compromised after five weeks of healing ($p<0.01$).

Conclusions: Based on biochemical analyses, histology, histomophometry, and ultrastructure, GDF-5 deficient mice Achilles tendons display a short term delay in healing of approximately one week. Ultrastructurally and biomechanically, the GDF-5 deficient tendons exhibit a long term delay in healing that is still evident after four weeks post-op. The observed abnormalities appear to be due to a delay in cellular recruitment and differentiation in the early stages of tendon repair in the absence of GDF-5. These results support the hypothesis that GDF-5/BMP-14 plays a role in Achilles tendon repair. Our findings suggest that GDF-5/BMP-14 may be a viable candidate for eventual therapeutic use to augment tendon repair in humans.

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Recombinant Human Bone Morphogenetic Protein-14 /CDMP-1

Description : BMPs (bone morphogenetic proteins) belong to th large group of growth and differentiation factors from the TGF-beta superfamily. These Ligands mediate numerous physiological processes. BMPs initiate, promote, and maintain cartilage and bone morphogenesis, differentiation and regeneration. The amino acid sequences of homologous BMPs from different mammalian species are highly conserved, some are even identical in several species e.g. mouse, rat and human BMP-2, and bovine and human BMP-10 and -11. BMP-14/CDM 1 is a principal initiator of cartilage development. BMP-14/CDMP-1 is predominantly expressed in long bones during human embryonic development Mutations of the BMP-14/CDMP-1 gene cause acromesomelic chondrodysplasia Hunter-Thompsc type dwarfism, characterized by short forearms, hands and feet. PeproTech's Recombinant Human BMP-14/CDMP-1 is a 13.5 kDa homodimeric disulfide-linked protein consisting of 121 amino acids.

Catalog #: 120-01

Source : *E.coli*

Formulation : The sterile filtered solution was lyophilized from 1 mM Sodium Citrate, pH 3.5.

Stability : The lyophilized protein is stable for a few weeks a room temperature, but best stored at -20^{0}C. Reconstituted BMP-14/CDMP-1 should be stored ii working aliquots at -20^{0}C.

Purity : Greater than 98% by SDS-PAGE. Endotoxin level less than 0.1 ng per µg (1EU/µg).

Reconstitution : We recommend a quick spin followed by reconstitution in water containing BSA (50µg of BSA per 1µg of protein) to a concentration of 0.1-1.0 mg/ml. This solution can then be diluted into other buffers and stored at 4^{0}C for 1 week or stored at -20^{0}C for future use.

Biological Activity : The **ED$_{50}$** was determined by its ability to induce alkaline phosphatase production by ATDC-5 chondrogenic cells is 1.0-2.0 µg/ml.

AA Sequence : MAPSATRQGK RPSKNLKARC SRKALHVNFK DMGWDDWIIA PLEYEAFHCE GLCEFPLRSH LEPTNHAVIQ TLMNSMDPES TPPTCCVPTR LSPISILFID SANNVVYKQY EDMVVESCGC R

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